We Claim:

1. A method for selecting an interacting pair of test polypeptides, comprising:

i providing a population of prokaryotic host cells wherein each host cell contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a first chimeric gene which encodes a first fusion protein, the first fusion protein including a DNA-binding domain and a first test polypeptide,

(c) a second chimeric gene which encodes a second fusion protein, the second fusion protein including an activation tag and second test polypeptide,

wherein the first fusion protein is part of a library of at least 10^7 members, the second fusion protein is part of a library of at least 10^7 members, or the first and second fusion proteins are both members of a library such that at least 10^7 unique pairs of test polypeptides could be tested for interaction;

wherein interaction of a first fusion protein and a second fusion protein in a host cell results in a desired level of expression of the reporter gene;

wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell; and

ii isolating host cells with a growth advantage wherein said cells comprise a first fusion protein and a second fusion protein which interact thereby selecting an interacting pair of test polypeptides.

2. The method of claim 1, which further comprises the step of identifying nucleic acids which encode test polypeptides which cause the desired level of expression of the reporter gene.

3. The method of claim 1, wherein selective growth conditions are applied to the host cells.

4. The method of claim 1, wherein the desired level of expression of the reporter gene is an increase in the level of expression of the reporter gene as compared to the basal expression level of the reporter gene.

5. The method of claim 1, wherein the transcriptional regulatory sequence includes at least two binding sites for a DNA-binding domain.

6. The method of claim 1, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

7. The method of claim 1, wherein the degree of the growth advantage conferred by the desired level of expression of the reporter gene is controllable by varying the growth conditions of the host cell.

8. The method of claim 7, wherein the reporter gene is the yeast His3 gene.

9. The method of claim 7, wherein the reporter gene is the yeast His3 gene and the degree of the growth advantage is controllable by exposing the host cell to varying concentrations of 3-aminotriazole.

10. The method of claim 7, wherein the reporter gene is a β-lactamase gene.

11. The method of claim 10, wherein the β-lactamase gene is selected from the group consisting of TEM-1, TEM-2, OXA-1, OXA-2, OXA-3, SHV-1, PSE-1, PSE-2, PSE-3, PSE-4 and CTX-1, and functional fragments thereof.

12. The method of claim 11, wherein the β-lactamase gene is TEM-1.

13. The method of claim 10, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic.

14. The method of claim 7, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic and varying concentrations of a β-lactamase inhibitor.

15. The method of claim 13, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems.

16. The method of claim 14, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems and the β-lactamase inhibitor is selected from the group consisting of Clavulanic acid, sulbactam, tazobactam, brobactam and β-lactamase inhibitory protein (BLIP).

17. The method of claim 1, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, a functional fragment of an RNA polymerase subunit, a molecule covalently fused to RNA polymerase, a molecule covalently fused to an RNA polymerase subunit, a molecule covalently fused to a functional fragment of RNA polymerase, or a molecule covalently fused to a functional fragment of an RNA polymerase subunit.

18. The method of claim 1, wherein the activation tag is a polypeptide, a nucleic acid, or a small molecule, and wherein the activation tag binds RNA polymerase, an RNA polymerase

subunit, a functional fragment of an RNA polymerase, or a functional fragment of an RNA polymerase subunit.

19. The method of claim 1, wherein the activation tag interacts indirectly with RNA polymerase via at least one intermediary polypeptide, nucleic acid, or small molecule, which functionally links the activation tag to the RNA polymerase.

20. The method of claim 18, wherein the activation tag is a fragment of Gal 11P, and wherein the activation tag interacts with a fusion between Gal4 and the α subunit of RNA polymerase.

21. The method of claim 1, wherein the prokaryotic host cell further contains a second reporter gene.

22. The method of claim 21, wherein interaction of first fusion protein and a second fusion protein in a host cell results in a desired level of expression of the second reporter gene.

23. The method of claim 22, wherein the desired level of expression of the second reporter gene is an increase in the level of expression of the reporter gene as compared to the basal expression level of the reporter gene.

24. The method of claim 22, wherein host cells are isolated that have one reporter gene whose expression level is increased to a greater extent than the increase in the expression level of the other reporter gene, as compared to the basal level of expression of the reporter genes.

25. The method of claim 21, wherein the first and second reporter genes are operably linked to the same transcriptional regulatory sequence.

26. The method of claim 21, wherein the first and second reporter genes are operably linked to separate copies of the same transcriptional regulatory sequence.

27. The method of claim 21, wherein the first and second reporter genes are operably linked to different transcriptional regulatory sequences.

28. The method of claim 21, wherein the second reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of color, fluorescence, luminescence, a cell surface tag, cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

29. The method of claim 28, wherein the second reporter gene confers a growth advantage under selective conditions different from the conditions used for the first reporter gene.

30. The method of claim 29, wherein the host cells containing a first and second fusion protein that interact are isolated by:

i selecting a first population of host cells with a desired expression level of the first reporter gene followed by selecting a second population of host cells from the first population of host cells based on a desired expression level of the second reporter gene;

ii selecting a first population of host cells with a desired expression level of the second reporter gene followed by selecting a second population of host cells from the first population of host cells based on a desired expression level of the first reporter gene; or

iii selecting a population of host cells based on simultaneous selection of desired expression levels of the first and second reporter genes.

31. The method of claim 28, wherein the second reporter gene is the lacZ gene.

32. The method of claim 28, wherein the second reporter gene encodes a fluorescent protein.

33. The method of claim 32, wherein the fluorescent protein is selected from the group consisting of green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), Renilla Reniformis green fluorescent protein, GFPmut2, GFPuv4, enhanced yellow fluorescent protein (EYFP), enhanced cyan fluorescent protein (ECFP), enhanced blue fluorescent protein (EBFP), citrine and red fluorescent protein from discosoma (dsRED).

34. The method of claim 28, wherein the second reporter gene encodes a protein which is expressed on the surface of the host cell.

35. The method of claim 34, further comprising the steps of:

iii contacting the host cell with a fluorescently labeled antibody specific for the protein encoded by the second reporter gene thereby labeling the host cell; and

iv isolating the cells expressing the second reporter gene using FACS analysis;

wherein steps iii and iv may occur before, after, or concurrently with step ii.

36. The method of claim 34, further comprising:

iii isolating host cells expressing the protein encoded by the second reporter gene using affinity chromatography,

wherein isolation of the host cells based on expression of the second reporter gene may occur before or after isolation of the host cells based on a desired level of expression of the first reporter gene.

37. The method of claim 36, wherein the affinity chromatography is carried out using a solid support or magnetic particles.

38. The method of claim 21, wherein the first reporter gene is selected from the group consisting of the yeast His3 gene and a β-lactamase gene and the second reporter gene is selected from the group consisting of the lacZ gene, a fluorescent protein, a protein which is expressed on the surface of the host cell and the bacterial aadA gene.

39. The method of claim 1, wherein the first and second fusion proteins are expressed from the same nucleic acid construct.

40. The method of claim 1, wherein the first and second fusion proteins are expressed from separate nucleic acid constructs.

41. The method of claim 1, wherein the expression level of the first, second, or first and second fusion proteins can be controlled by varying the growth conditions of the host cell.

42. The method of claim 41, wherein the expression level of the first and second fusion proteins can be controlled by varying the concentration of IPTG, anhydrotetracycline, or IPTG and anhydrotetracycline to which the host cell is exposed.

43. The method of claim 42, wherein the first, second, or first and second fusion proteins are expressed from a promoter comprising a binding site for the lac repressor or the tet repressor.

44. The method of claim 41, wherein the expression level of the first and second fusion protein can be independently controlled.

45. The method of claim 1, wherein the first fusion protein is part of a library of at least 10^8 members, the second fusion protein is part of a library of at least 10^8 members, or the first and second fusion proteins are both members of a library such that at least 10^8 unique pairs of test polypeptides could be tested for interaction.

46. The method of claim 1, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

47. The method of claim 1, wherein (a), (b), or (c), or any combination thereof, are contained within one or more vectors for introduction into the host cell.

48. The method of claim 47, wherein the vector is a phagemid and is introduced into the host cell by infection of the host cell with infectious phage containing the phagemid vector.

49. A method for identifying agents which modulate a protein-protein interaction, comprising:

i providing a population of prokaryotic host cells wherein each host cell contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a first chimeric gene which encodes a first fusion protein, the first fusion protein including a DNA-binding domain and a first test polypeptide,

(c) a second chimeric gene which encodes a second fusion protein, the second fusion protein including an activation tag and second test polypeptide,

wherein the prokaryotic host cell is an imp$^-$ or gram positive strain of bacteria;

wherein interaction of a first fusion protein and a second fusion protein in a host cell results in a desired level of expression of the reporter gene;

ii contacting the host cell with at least one test agent; and

iii identifying test agents which modulate expression of the reporter gene in a manner also dependent on the expression of the first and second test polypeptides, thereby identifying agents which modulate a protein-protein interaction.

50. The method of claim 49, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of color, fluorescence, luminescence, a cell surface tag, cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

51. The method of claim 49, which further comprises comparing the level of expression of the reporter gene to a level of expression in a control experiment wherein one or both of the test polypeptides are absent or altered so as to preclude interaction of the first and second fusion proteins.

52. The method of claim 49, wherein the test agent is selected from the group consisting of peptides, nucleic acids, carbohydrates, natural product extract libraries, and small organic molecules.

53. The method of claim 49, wherein the test agent is part of a library of test agents.

54. The method of claim 53, wherein the library of test agents has at least 10^7 members.

55. The method of claim 49, wherein test agents are identified which agonize the protein-protein interaction based on a change in the expression level of the reporter gene in the presence of the test agent.

56. The method of claim 49, wherein test agents are identified which antagonize the protein-protein interaction based on a change in the expression level of the reporter gene in the presence of the test agent.

57. The method of claim 49, wherein the host cells are grown under conditions which increase the permeability of the cell membrane.

58. A method for selecting a polypeptide which differentially interacts with at least two different test polypeptides, comprising:

i providing a population of prokaryotic host cells wherein each cell contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a first DNA-binding domain,

(b) a second reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a second DNA-binding domain,

(c) a first chimeric gene which encodes a first fusion protein, the first fusion protein including a first DNA-binding domain and a first test polypeptide,

(d) a second chimeric gene which encodes a second fusion protein, the second fusion protein including a second DNA-binding domain and a second test polypeptide,

(e) a third chimeric gene which encodes a third fusion protein, the third fusion protein including an activation tag and third test polypeptide,

wherein the third fusion protein is part of a library of at least 10^7 members;

wherein interaction of the first fusion protein and the third fusion protein in the host cell results in a desired level of expression of the first reporter gene;

wherein interaction of the second fusion protein and the third fusion protein in the host cell results in a desired level of expression of the second reporter gene; and

ii isolating host cells comprising a third fusion protein capable of interacting with the first fusion protein, the second fusion protein, or the first and the second fusion proteins based on a desired level of expression of the first reporter gene, the second reporter gene, or the first and second reporter genes, respectively, thereby

selecting a polypeptide which differentially interacts with at least two different test polypeptides.

59. The method of claim 58, wherein host cells are isolated which comprise a third fusion protein that interacts with both the first and second fusion proteins.

60. The method of claim 58, wherein host cells are isolated which comprise a third fusion protein that interacts to a greater extent with one of the peptides as compared to the other polypeptide.

61. The method of claim 58, wherein the host cell further comprises

(e) a third reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site (DBD recognition element) for a third DNA-binding domain,

(f) a fourth chimeric gene which encodes a fourth fusion protein including a third DNA-binding domain and a fourth test polypeptide,

wherein interaction of the fourth fusion protein and the third fusion protein in the host cell results in a desired level of expression of the third reporter gene; and

wherein step ii further comprises isolating host cells comprising the third fusion protein interacting with a fourth fusion protein based on a desired level of expression of the first, second and third reporter genes.

62. The method of claim 61, wherein the host cell further comprises

(g) a fourth reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site (DBD recognition element) for a fourth DNA-binding domain,

(h) a fifth chimeric gene which encodes a fifth fusion protein including a fourth DNA-binding domain and a fifth test polypeptide,

wherein interaction of the fifth fusion protein and the third fusion protein in the host cell results in a desired level of expression of the fourth reporter gene; and

wherein step ii further comprises isolating host cells comprising the third fusion protein interacting with a fifth fusion protein based on a desired level of expression of the first, second, third and fourth reporter genes.

63. The method of claim 62, wherein the host cell further comprises

(i) a fifth reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site (DBD recognition element) for a fifth DNA-binding domain,

(j) a sixth chimeric gene which encodes a sixth fusion protein including a fifth DNA-binding domain and a fifth test polypeptide,

wherein interaction of the sixth fusion protein and the third fusion protein in the host cell results in a desired level of expression of the fifth reporter gene; and

wherein step ii further comprises isolating host cells comprising the third fusion protein interacting with a sixth fusion protein based on a desired level of expression of the first, second, third, fourth and fifth reporter genes.

64. The method of any one of claims 58 or 61-63, wherein host cells are isolated

(i) which comprise a third fusion protein that interacts to a desired extent with all of the other fusion proteins;

(ii) which comprise a third fusion protein that interacts with one of the polypeptides to a greater extent than it interacts with the other fusion proteins; or

(iii) which comprise a third fusion protein that interacts to a desired extent with a desired combination of at least two of the other fusion proteins.

65. The method of any one of claims 58 or 61-63, wherein the desired level of expression of at least one of the reporter genes is an increase in the level of expression of the reporter gene as compared to the basal expression level of the reporter gene.

66. The method of any one of claims 58 or 61-63, wherein the reporter genes encode unique detectable proteins which can be analyzed independently, simultaneously, or independently and simultaneously.

67. The method of claim 66, wherein at least one of the reporter genes encodes a fluorescent protein.

68. The method of claim 66, wherein the expression level of at least one of the reporter genes is analyzed by FACS.

69. The method of any one of claims 58 or 61-63, which further comprises the step of identifying nucleic acids which encode fusion proteins resulting in a desired level of expression of a reporter gene.

70. A method for selecting a test agent that differentially modulates the interaction of a polypeptide with at least two different test polypeptides, comprising:

i providing a population of prokaryotic host cells wherein each cell contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a first DNA-binding domain,

(b) a second reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a second DNA-binding domain,

(c) a first chimeric gene which encodes a first fusion protein, the first fusion protein including a first DNA-binding domain and a first test polypeptide,

(d) a second chimeric gene which encodes a second fusion protein, the second fusion protein including a second DNA-binding domain and a second test polypeptide,

(e) a third chimeric gene which encodes a third fusion protein, the third fusion protein including an activation tag and third test polypeptide,

wherein the host cell is an imp^{-} or gram positive strain of bacteria;

wherein interaction of the first fusion protein and the third fusion protein in the host cell results in a desired level of expression of the first reporter gene;

wherein interaction of the second fusion protein and the third fusion protein in the host cell results in a desired level of expression of the second reporter gene;

ii contacting the host cell with at least one test agent; and

iii identifying test agents which modulate the expression of the first, second, or first and second reporter genes in a manner also dependent on the expression of the first, second and third test polypeptides, thereby selecting a test agent that differentially modulates the interaction of a polypeptide with at least two different test polypeptides.

71. A method for detecting an interaction between a test polypeptide and a DNA sequence, comprising

i providing a population of prokaryotic host cells wherein each cell contains

(a) a reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a chimeric gene which encodes a fusion protein, the fusion protein including a test polypeptide and an activation tag,

wherein the DBD recognition element is part of a library of at least 10^7 members, the fusion protein is part of a library of at least 10^7 members, or the DBD recognition element and the fusion protein are both members of a library such that at least 10^7 unique pairs of a DBD recognition element and a fusion protein could be tested for interaction;

wherein interaction between a test polypeptide of a fusion protein and a DBD recognition element in a host cell results in a desired level of expression of the reporter gene;

wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell; and

ii isolating host cells with a growth advantage wherein said cells comprise a fusion protein and a DBD recognition element which interact, thereby detecting an interaction between a test polypeptide and a DNA sequence.

72. The method of claim 71, further comprising the step of identifying the nucleic acid which encodes a test polypeptide that interacts with the DBD recognition element DNA sequence.

73. The method of claim 71, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, or a functional fragment of an RNA polymerase subunit.

74. The method of claim 71, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, a functional fragment of an RNA polymerase subunit, a molecule covalently fused to RNA polymerase, a molecule covalently fused to an RNA polymerase subunit, a molecule covalently fused to a functional fragment of RNA polymerase, or a molecule covalently fused to a functional fragment of an RNA polymerase subunit.

75. The method of claim 71, wherein the activation tag interacts indirectly with RNA polymerase via at least one intermediary polypeptide, nucleic acid, or small molecule, which functionally links the activation tag to the RNA polymerase.

76. The method of claim 74, wherein the activation tag is a fragment of Gal 11P, and wherein the activation tag interacts with a fusion between Gal4 and the α subunit of RNA polymerase.

77. The method of claim 71, wherein (a), (b), or (a) and (b), are contained within one or more vectors for introduction into the host cell.

78. The method of claim 71, wherein the growth advantage is selected from the group consisting of cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

79. The method of claim 71, wherein the degree of the growth advantage conferred by the desired level of expression of the reporter gene is controllable by varying the growth conditions of the host cell.

80. The method of claim 79, wherein the reporter gene is the yeast His3 gene.

81. The method of claim 79, wherein the reporter gene is the yeast His3 gene and the degree of the growth advantage is controllable by exposing the host cell to varying concentrations of 3-aminotriazole.

82. The method of claim 79, wherein the reporter gene is a β-lactamase gene.

83. The method of claim 82, wherein the β-lactamase gene is selected from the group consisting of TEM-1, TEM-2, OXA-1, OXA-2, OXA-3, SHV-1, PSE-1, PSE-2, PSE-3, PSE-4 and CTX-1, and functional fragments thereof.

84. The method of claim 83, wherein the β-lactamase gene is TEM-1.

85. The method of claim 82, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic.

86. The method of claim 79, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic and varying concentrations of a β-lactamase inhibitor.

87. The method of claim 85, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems.

88. The method of claim 86, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems and the β-lactamase inhibitor is selected from the group consisting of Clavulanic acid, sulbactam, tazobactam, brobactam and β-lactamase inhibitory protein (BLIP).

89. The method of claim 71, wherein the DBD recognition element is a member of a library of at least 10^7 potential binding sites for a DNA binding domain, wherein host cells comprising a DBD recognition element bound by a test polypeptide are isolated.

90. The method of claim 89, wherein the polypeptide is a zinc finger protein.

91. The method of claim 71, wherein the DBD recognition element is a desired binding site for a DNA binding domain and the test polypeptide is a member of a library of at least 10^7 polypeptides, wherein host cells comprising a polypeptide which binds to the DBD recognition element are isolated.

92. The method of claim 71, wherein the DBD recognition element is a desired binding site for a DNA binding domain and the test polypeptide is a member of a library of at least 10^8 polypeptides, wherein host cells comprising a polypeptide which binds to the DBD recognition element are isolated.

93. The method of claim 91, wherein the polypeptides are zinc finger proteins.

94. The method of claim 71, wherein the DBD recognition element is a member of library of potential binding sites for a DNA binding domain and the test polypeptide is a member of a library of polypeptides, wherein host cells comprising a polypeptide that binds a DBD recognition element are isolated.

95. The method of claim 94, wherein the polypeptides are zinc finger proteins.

96. A polypeptide isolated by the method of any one of claims 91, 92 or 94.

97. The polypeptide of claim 96 which is a zinc finger protein.

98. A binding site for a DNA binding domain isolated by the method of any one of claims 89 or 94.

99. The binding site for a DNA binding domain of claim 98 which binds a zinc finger protein.

100. An interacting pair of a polypeptide and a binding site for a DNA binding domain isolated by the method of claim 94.

101. The interacting pair of claim 100, wherein the polypeptide is a zinc finger protein.

102. A method for identifying agents which modulate an interaction between a test polypeptide and a DNA sequence, comprising

i providing a population of prokaryotic host cells wherein each cell contains

(a) a reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a chimeric gene which encodes a fusion protein, the fusion protein including a test polypeptide and an activation tag,

wherein the prokaryotic host cell is an imp$^-$ or gram positive strain of bacteria;

wherein interaction between a test polypeptide of a fusion protein and a DBD recognition element in a host cells results in a desired level of expression of the reporter gene;

ii contacting the host cell with at least one test agent; and

iii identifying agents which modulate expression of the reporter gene in a manner also dependent on the presence of a fusion protein and a DBD recognition element.

103. The method of claim 102, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of color, fluorescence, luminescence, a cell surface tag, cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

104. The method of claim 102, wherein the DBD recognition element is part of a library of at least 10^7 members, the fusion protein is part of a library of at least 10^7 members, or the DBD recognition element and the fusion protein are both members of a library such that at least 10^7 unique pairs of a DBD recognition element and a fusion protein could be tested for interaction.

105. The method of claim 102, which further comprises comparing the level of expression of the reporter gene to a level of expression in a control experiment wherein one or both of the test polypeptide and the DBD recognition element are absent or altered so as to preclude interaction of the fusion protein and the DBD recognition element.

106. The method of claim 102, wherein the test agent is selected from the group consisting of peptides, nucleic acids, carbohydrates, natural product extract libraries, and small organic molecules.

107. The method of claim 102, wherein the test agent is part of a library of test agents.

108. The method of claim 102, wherein test agents are identified which agonize the protein-nucleic acid interaction based on a change in the expression level of the reporter gene in the presence of the test agent.

109. The method of claim 102, wherein test agents are identified which antagonize the protein-nucleic acid interaction based on a change in the expression level of the reporter gene in the presence of the test agent.

110. The method of claim 102, wherein the host cells are grown under conditions which increase the permeability of the cell membrane.

111. A method for selecting a polypeptide that differentially interacts with at least two different DNA sequences, comprising

i providing a population of prokaryotic host cells each of which contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a first DNA-binding domain,

(b) a second reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding site (DBD recognition element) for a second DNA-binding domain,

(c) a chimeric gene which encodes a fusion protein, the fusion protein including a test polypeptide and an activation tag,

wherein the fusion protein is part of a library of at least 10^7 members;

wherein interaction of a fusion protein with the first DBD recognition element in the host cells results in a desired level of expression of the first reporter gene;

wherein interaction of a fusion protein with the second DBD recognition element in the host cells results in a desired level of expression of the second reporter gene; and

ii isolating host cells comprising a fusion protein that interacts with the first DBD recognition element, the second DBD recognition element, or the first and second DBD recognition elements based on a desired level of expression of the first reporter gene, the second reporter gene, or the first and second reporter genes, respectively, thereby selecting a polypeptide that differentially interacts with at least two different DNA sequences.

112. The method of claim 111, wherein the fusion protein is assayed for the ability to interact with at least three different DNA sequences each operably linked to different reporter genes.

113. The method of claim 111, wherein the first and second reporter genes are operably linked to the same transcriptional regulatory sequence.

114. The method of claim 111, wherein the first and second reporter genes are operably linked to separate copies of the same transcriptional regulatory sequence.

115. The method of claim 111, wherein the first and second reporter genes are operably linked to different transcriptional regulatory sequences.

116. The method of any one of claims 111-115, wherein all of the reporter genes encode different proteins and each reporter gene may be detected independently, simultaneously, or independently and simultaneously.

117. The method of any one of claims 111-115, which further comprises the step of isolating the nucleic acid which encodes the fusion protein.

118. The method of any one of claims 111-115, wherein host cells are isolated that have one reporter gene whose expression level is increased to a greater extent than the increase in the expression level of the other reporter genes, as compared to the basal level of expression of the reporter genes.

119. A method for selecting a test agent that differentially modulates the interaction of a polypeptide with at least two different DNA sequences, comprising

i providing a population of prokaryotic host cells each of which contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a first DNA-binding domain,

(b) a second reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding site (DBD recognition element) for a second DNA-binding domain,

(c) a chimeric gene which encodes a fusion protein, the fusion protein including a test polypeptide and an activation tag,

wherein the prokaryotic host cell is an imp^- or gram positive strain of bacteria;

wherein interaction of a fusion protein with the first DBD recognition element in the host cells results in a desired level of expression of the first reporter gene;

wherein interaction of a fusion protein with the second DBD recognition element in the host cells results in a desired level of expression of the second reporter gene;

ii contacting the host cell with at least one test agent; and

iii identifying test agents which modulate the expression of the first, second, or first and second reporter genes in a manner also dependent on the presence of the fusion protein and the first and second DBD recognition elements, thereby selecting a test agent that differentially modulates the interaction of a polypeptide with at least two different DNA sequences.

120. The method of claim 119, wherein the DBD recognition element is part of a library of at least 10^7 members, the fusion protein is part of a library of at least 10^7 members, or the DBD recognition element and the fusion protein are both members of a library such that at least 10^7 unique pairs of a DBD recognition element and a fusion protein could be tested for interaction.

121. A method for detecting an interaction between a test RNA binding domain polypeptide and an RNA sequence, comprising

i providing a population of prokaryotic host cells wherein each cell contains

(a) a reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a first chimeric gene which encodes a fusion protein, the fusion protein including a DNA-binding domain and a first RNA binding domain,

(c) a second chimeric gene which encodes a fusion protein, the fusion protein including an activation tag and a second RNA binding domain,

(d) a third chimeric gene which encodes a hybrid RNA, the hybrid RNA comprising a first RNA sequence that binds one of the first or second RNA binding domains and a second RNA sequence to be tested for interaction with the RNA-binding domain not bound to the first RNA sequence;

wherein the RNA-binding domain not bound to the first RNA sequence is part of a library of at least 10^7 members, the second RNA sequence is part of a library of at least 10^7 members, or the RNA-binding domain not bound to the first RNA sequence and the second RNA sequence are both members of a library such that at least 10^7 unique pairs of an RNA-binding domain and an RNA sequence could be tested for interaction;

wherein interaction of an RNA-binding domain not bound to the first RNA sequence with the second RNA sequence in a host cell results in a desired level of expression of the reporter gene; and

ii isolating host cells comprising an RNA-binding domain that interacts with the second RNA sequence based on a desired level of expression of the reporter gene thereby

detecting an interaction between a test RNA binding domain polypeptide and an RNA sequence.

122. A kit for selecting a polypeptide that interacts with a test polypeptide, comprising:

i a first gene construct for encoding a first fusion protein, which first gene construct comprises:

(a) transcriptional and translational elements which direct expression of a protein in a prokaryotic host cell,

(b) a DNA sequence that encodes a DNA binding domain and which is operably linked with the transcriptional and translational elements of the first gene construct, and

(c) one or more sites for inserting a DNA sequence encoding a first test polypeptide into the first gene construct in such a manner that the first test polypeptide is expressed in-frame as part of a fusion protein containing the DNA binding domain;

ii a second gene construct for encoding a second fusion protein, which second gene construct comprises:

(a) transcriptional and translational elements which direct expression of a protein in a prokaryotic host cell,

(b) a DNA sequence that encodes an activation tag and which is operably linked with the transcriptional and translational elements of the second gene construct, and

(c) one or more sites for inserting a DNA sequence encoding a second test polypeptide into the second gene construct in such a manner that the second test polypeptide is expressed in-frame as part of a fusion protein containing the activation tag; and

iii a prokaryotic host cell containing at least one reporter gene having one or more binding sites (DBD recognition elements) for the DNA binding domain, and

wherein a desired level of expression of the reporter gene is obtained upon interaction of the first and second fusion proteins; and

wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell.

123. The kit of claim 122, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

124. The kit of claim 122, wherein the degree of the growth advantage conferred by the desired level of expression of the reporter gene is controllable by varying the growth conditions of the host cell.

125. The kit of claim 124, wherein the reporter gene is the yeast His3 gene.

126. The kit of claim 124, wherein the reporter gene is the yeast His3 gene and the degree of the growth advantage is controllable by exposing the host cell to varying concentrations of 3-aminotriazole.

127. The kit of claim 124, wherein the reporter gene is a β-lactamase gene.

128. The kit of claim 127, wherein the β-lactamase gene is selected from the group consisting of TEM-1, TEM-2, OXA-1, OXA-2, OXA-3, SHV-1, PSE-1, PSE-2, PSE-3, PSE-4 and CTX-1, and functional fragments thereof.

129. The kit of claim 128, wherein the β-lactamase gene is TEM-1.

130. The kit of claim 127, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic.

131. The kit of claim 124, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic and varying concentrations of a β-lactamase inhibitor.

132. The kit of claim 130, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems.

133. The kit of claim 131, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems and the β-lactamase inhibitor is selected from the group consisting of Clavulanic acid, sulbactam, tazobactam, brobactam and β-lactamase inhibitory protein (BLIP).

134. The kit of claim 122, wherein the first gene construct, the second gene construct, or the first and second gene constructs, are contained within a phagemid vector.

135. A test polypeptide isolated using the kit of claim 122.

136. A kit for detecting an interaction between a test DNA-binding domain polypeptide and a DNA sequence, comprising:

i a first gene construct which comprises:

(a) one or more sites for inserting a DNA sequence comprising a transcriptional element which includes at least one binding site (DBD recognition element) for a DNA-binding domain,

(b) a translational element operably linked to the transcriptional element, and

(c) a DNA sequence for a reporter gene which is operably linked with the transcriptional and translational elements of the first gene construct, and

wherein the transcriptional and translational elements direct expression of the reporter gene in a prokaryotic host cell;

ii a second gene construct for encoding a first fusion protein, which second gene construct comprises:

(a) transcriptional and translational elements which direct expression of a protein in a prokaryotic host cell,

(b) a DNA sequence that encodes an activation tag and which is operably linked with the transcriptional and translational elements of the second gene construct, and

(c) one or more sites for inserting a DNA sequence encoding a first test polypeptide into the second gene construct in such a manner that the first test polypeptide is expressed in-frame as part of a fusion protein containing the activation tag;

iii a prokaryotic host cell, and

wherein a desired level of expression of the reporter gene is obtained upon interaction of a test polypeptide with a DBD recognition element; and

wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell.

137. The kit of claim 136, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of cell viability, relief of a cell nutritional requirement, cell growth and drug resistance.

138. The kit of claim 136, wherein the degree of the growth advantage conferred by the desired level of expression of the reporter gene is controllable by varying the growth conditions of the host cell.

139. The kit of claim 138, wherein the reporter gene is the yeast His3 gene.

140. The kit of claim 138, wherein the reporter gene is the yeast His3 gene and the degree of the growth advantage is controllable by exposing the host cell to varying concentrations of 3-aminotriazole.

141. The kit of claim 138, wherein the reporter gene is a β-lactamase gene.

142. The kit of claim 141, wherein the β-lactamase gene is selected from the group consisting of TEM-1, TEM-2, OXA-1, OXA-2, OXA-3, SHV-1, PSE-1, PSE-2, PSE-3, PSE-4 and CTX-1, and functional fragments thereof.

143. The kit of claim 142, wherein the β-lactamase gene is TEM-1.

144. The kit of claim 141, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic.

145. The kit of claim 138, wherein the reporter gene is a β-lactamase gene and the degree of the growth advantage is controllable by exposing the host cell to a β-lactam antibiotic and varying concentrations of a β-lactamase inhibitor.

146. The kit of claim 144, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems.

147. The kit of claim 145, wherein the β-lactam antibiotic is selected from the group consisting of penicillins, cephalosporins, monbactams and carbapenems and the β-lactamase inhibitor is selected from the group consisting of Clavulanic acid, sulbactam, tazobactam, brobactam and β-lactamase inhibitory protein (BLIP).

148. The kit of claim 136, wherein the first gene construct, the second gene construct, or the first and second gene constructs, are contained within a phagemid vector.

149. The kit of claim 136, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, or a functional fragment of an RNA polymerase subunit.

150. The kit of claim 136, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, a functional fragment of an RNA polymerase subunit, a molecule covalently fused to RNA polymerase, a molecule covalently fused to an RNA polymerase subunit, a molecule covalently fused to a functional fragment of RNA polymerase, or a molecule covalently fused to a functional fragment of an RNA polymerase subunit.

151. The kit of claim 136, wherein the activation tag interacts indirectly with RNA polymerase via at least one intermediary polypeptide, nucleic acid, or small molecule, which functionally links the activation tag to the RNA polymerase.

152. The kit of claim 136, wherein the activation tag is a fragment of Gal 11P, and wherein the activation tag interacts with a fusion between Gal4 and the α subunit of RNA polymerase.

153. The kit of claim 136, wherein the desired level of expression of the reporter gene confers a growth advantage to the host cells.

154. A test DNA-binding domain polypeptide isolated using the kit of claim 136.

155. The DNA-binding domain polypeptide of claim 154, which is a zinc finger protein.

156. A binding site for a DNA binding domain isolated using the kit of claim 136.

157. The binding site for a DNA binding domain of claim 156 that binds a zinc finger protein.

158. An interacting pair of a polypeptide and a binding site for a DNA binding domain isolated using the kit of claim 136.

159. The interacting pair of claim 158, wherein the polypeptide is a zinc finger protein.

160. A method for detecting an interaction between a first test polypeptide and a second test polypeptide, comprising:

i providing a population of host cells wherein each cell contains

(a) a reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a first chimeric gene which encodes a first fusion protein, the first fusion protein including a DNA-binding domain and a first test polypeptide,

(c) a second chimeric gene which encodes a second fusion protein, the second fusion protein including an activation tag and second test polypeptide,

wherein expression of the reporter gene results in signal detectable by FACS;

wherein interaction of the first fusion protein and second fusion protein in the host cell results in a desired level of expression of the reporter gene; and

ii isolating host cells comprising an interacting pair of fusion proteins based on a desired level of expression of the reporter gene using FACS thereby detecting an interaction between a first test polypeptide and a second test polypeptide.

161. The method of claim 160, which further comprises the step of isolating the nucleic acid which encodes the test polypeptides.

162. The method of claim 160, wherein the first, second, or first and second fusion proteins are members of a library.

163. The method of claim 162, wherein the first fusion protein is part of a library of at least 10^7 members, the second fusion protein is part of a library of at least 10^7 members, or the first and second fusion proteins are both members of a library such that at least 10^7 unique pairs of test polypeptides could be tested for interaction.

164. The method of claim 160, wherein the host cell is a eukaryotic cell.

165. The method of claim 164, wherein the host cell is a yeast cell.

166. The method of claim 160, wherein the host cell is a prokaryotic cell.

167. The method of claim 166, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

168. The method of claim 160, wherein the desired level of expression of the reporter gene is an increase in the level of expression of the reporter gene as compared to the basal expression level of the reporter gene.

169. The method of claim 160, wherein the transcriptional regulatory sequence includes at least two binding sites for a DNA-binding domain.

170. The method of claim 160, wherein the transcriptional regulatory sequence includes at least three binding sites for a DNA-binding domain.

171. The method of claim 160, wherein the reporter gene encodes a protein product which gives rise to a detectable signal selected from the group consisting of fluorescence, luminescence and a cell surface tag.

172. The method of claim 171, wherein the reporter gene encodes a fluorescent protein selected from the group consisting of green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), Renilla Reniformis green fluorescent protein, GFPmut2, GFPuv4, enhanced yellow fluorescent protein (EYFP), enhanced cyan fluorescent protein (ECFP), enhanced blue fluorescent protein (EBFP), citrine and red fluorescent protein from discosoma (dsRED).

173. The method of claim 171, wherein the reporter gene encodes a cell surface tag and the method further comprises the step of contacting the host cell with a fluorescently labeled antibody specific for the cell surface tag, thereby labeling the host cell, before isolation of host cells by FACS.

174. The method of claim 160, wherein the host cell further contains a second reporter gene.

175. The method of claim 174, wherein interaction of first fusion protein and a second fusion protein in a host cell results in a desired level of expression of the second reporter gene.

176. The method of claim 175, wherein the desired level of expression of the second reporter gene is an increase in the level of expression of the reporter gene as compared to the basal expression level of the reporter gene.

177. The method of claim 175, wherein the desired level of expression of the first reporter gene is an increase in the expression level of the first reporter gene as compared to the basal expression level of the first reporter gene, and the desired level of expression of the second reporter gene is a smaller increase in the expression level of the second reporter gene as compared to the basal expression level of the second reporter gene relative to the increase in expression of the first reporter gene.

178. The method of claim 174, wherein the first and second reporter genes are operably linked to the same transcriptional regulatory sequence.

179. The method of claim 174, wherein the first and second reporter genes are operably linked to separate copies of the same transcriptional regulatory sequence.

180. The method of claim 174, wherein the first and second reporter genes are operably linked to separate copies of different transcriptional regulatory sequences.

181. The method of claim 174, wherein the second reporter gene encodes a protein product which gives rise to a detectable signal selected from the group consisting of fluorescence, luminescence and a cell surface tag.

182. The method of claim 181, wherein the second reporter gene encodes a fluorescent protein selected from the group consisting of green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), Renilla Reniformis green fluorescent protein, GFPmut2, GFPuv4, enhanced yellow fluorescent protein (EYFP), enhanced cyan fluorescent protein (ECFP), enhanced blue fluorescent protein (EBFP), citrine and red fluorescent protein from discosoma (dsRED).

183. The method of claim 181, wherein the second reporter gene encodes a cell surface tag and the method further comprises the step of contacting the host cell with a fluorescently

labeled antibody specific for the cell surface tag, thereby labeling the host cell, before isolation of host cells by FACS.

184. The method of claim 174, wherein the first and second reporter genes encode proteins which can be analyzed independently, simultaneously, or independently and simultaneously

185. The method of claim 160, wherein the first and second fusion proteins are expressed from the same nucleic acid construct.

186. The method of claim 160, wherein the first and second fusion proteins are expressed from separate nucleic acid constructs.

187. The method of claim 160, wherein the expression level of the first, second, or first and second fusion proteins can be controlled by varying the growth conditions of the host cell.

188. The method of claim 187, wherein the expression level of the first and second fusion proteins can be controlled by varying the concentration of IPTG, anhydrotetracycline, or IPTG and anhydrotetracycline to which the host cell is exposed.

189. The method of claim 188, wherein the first, second, or first and second fusion proteins are expressed from a promoter comprising a binding site for the lac repressor or the tet repressor.

190. The method of claim 187, wherein the expression level of the first and second fusion proteins can be independently controlled.

191. A method for selecting a polypeptide that differentially interacts with at least two different test polypeptides, comprising:

i providing a population of host cells wherein each cell contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a first DNA-binding domain,

(b) a second reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a second DNA-binding domain,

(c) a first chimeric gene which encodes a first fusion protein, the first fusion protein including a first DNA-binding domain and a first test polypeptide,

(d) a second chimeric gene which encodes a second fusion protein, the second fusion protein including a second DNA-binding domain and a second test polypeptide,

(e) a third chimeric gene which encodes a third fusion protein, the third fusion protein including an activation tag and third test polypeptide,

wherein expression of the first and second reporter genes results in a signal detectable by FACS;

wherein interaction of the first fusion protein and the third fusion protein in the host cell results in a desired level of expression of the first reporter gene;

wherein interaction of the second fusion protein and the third fusion protein in the host cell results in a desired level of expression of the second reporter gene; and

ii isolating host cells comprising a third fusion protein capable of interacting with the first fusion protein, the second fusion protein, or the first and the second fusion proteins based on a desired level of expression of the first reporter gene, the second reporter gene, or the first and second reporter genes, respectively, using FACS, thereby selecting a polypeptide that differentially interacts with at least two different test polypeptides.

192. The method of claim 191, wherein host cells are isolated which comprise a third fusion protein that interacts with both the first and second fusion proteins.

193. The method of claim 191, wherein host cells are isolated which comprise a third fusion protein that interacts with only one of the first or second fusion proteins.

194. The method of claim 191, wherein the host cell further comprises

(e) a third reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site (DBD recognition element) for a third DNA-binding domain,

(f) a fourth chimeric gene which encodes a fourth fusion protein including a third DNA-binding domain and a fourth test polypeptide,

wherein expression of the third reporter gene results in a signal detectable by FACS;

wherein interaction of the fourth fusion protein and the third fusion protein in the host cell results in a desired level of expression of the third reporter gene; and

wherein step ii further comprises isolating host cells comprising the third fusion protein interacting with a fourth fusion protein based on a desired level of expression of the first, second and third reporter genes using FACS.

195. The method of claim 194, wherein the host cell further comprises

(g) a fourth reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site (DBD recognition element) for a fourth DNA-binding domain,

(h) a fifth chimeric gene which encodes a fifth fusion protein including a fourth DNA-binding domain and a fifth test polypeptide,

wherein expression of the fourth reporter gene results in a signal detectable by FACS;

wherein interaction of the fifth fusion protein and the third fusion protein in the host cell results in a desired level of expression of the fourth reporter gene; and

wherein step ii further comprises isolating host cells comprising the third fusion protein interacting with a fifth fusion protein based on a desired level of expression of the first, second, third and fourth reporter genes using FACS.

196. The method of claim 195, wherein the host cell further comprises

(i) a fifth reporter gene operably linked to a transcriptional regulatory sequence which includes a binding site (DBD recognition element) for a fifth DNA-binding domain,

(j) a sixth chimeric gene which encodes a sixth fusion protein including a fifth DNA-binding domain and a fifth test polypeptide,

wherein expression of the fifth reporter gene results in a signal detectable by FACS;

wherein interaction of the sixth fusion protein and the third fusion protein in the host cell results in a desired level of expression of the fifth reporter gene; and

wherein step ii further comprises isolating host cells comprising the third fusion protein interacting with a sixth fusion protein based on a desired level of expression of the first, second, third, fourth and fifth reporter genes using FACS.

197. The method of any one of claims 191 or 194-196, wherein host cells are isolated which comprise a third fusion protein that interacts to a desired extent with all of the other fusion proteins.

198. The method of any one of claims 191 or 194-196, wherein host cells are isolated which comprise a third fusion protein that interacts with one of the fusions proteins to a greater extent than it interacts with the other fusion proteins.

199. The method of any one of claims 191 or 194-196, wherein host cells are isolated which comprise a third fusion protein that interacts to a desired extent with a desired combination of at least two of the other fusion proteins.

200. The method of any one of claims 191 or 194-196, which further comprises the step of identifying nucleic acids which encode fusion proteins resulting in a desired level of expression of a reporter gene.

201. The method of claim 191, wherein the host cell is a eukaryotic cell.

202. The method of claim 201, wherein the host cell is a yeast cell.

203. The method of claim 191, wherein the host cell is a prokaryotic cell.

204. The method of claim 203, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and Shigella.

205. A method for detecting an interaction between a test polypeptide and a DNA sequence, comprising

i providing a population of host cells wherein each cell contains

(a) a reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a chimeric gene which encodes a fusion protein, the fusion protein including a test polypeptide and an activation tag,

wherein expression of the reporter gene results in signal detectable by FACS;

wherein interaction between a test polypeptide of a fusion protein and a DBD recognition element in a host cells results in a desired level of expression of the reporter gene; and

ii isolating host cells comprising a fusion protein that interacts with a DBD recognition element based on a desired level of expression of the reporter gene using FACS thereby detecting an interaction between the test polypeptide and the DBD recognition element DNA sequence.

206. The method of claim 205, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, or a functional fragment of an RNA polymerase subunit.

207. The method of claim 205, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, a functional fragment of an RNA polymerase subunit, a molecule covalently fused to RNA polymerase, a molecule covalently fused to an RNA polymerase subunit, a molecule covalently fused to a functional fragment of RNA polymerase, or a molecule covalently fused to a functional fragment of an RNA polymerase subunit.

208. The method of claim 205, wherein the activation tag interacts indirectly with RNA polymerase via at least one intermediary polypeptide, nucleic acid, or small molecule, which functionally links the activation tag to the RNA polymerase.

209. The method of claim 207, wherein the activation tag is a fragment of Gal 11P, and wherein the activation tag interacts with a fusion between Gal4 and the α subunit of RNA polymerase.

210. The method of claim 205, which further comprises the step of isolating the nucleic acid which encodes the test polypeptides.

211. The method of claim 205, wherein DBD recognition element, the fusion protein, or the DBD recognition element and the fusion protein are members of a library.

212. The method of claim 211, wherein the DBD recognition element is part of a library of at least 10^7 members, the fusion protein is part of a library of at least 10^7 members, or the DBD recognition element and the fusion protein are both members of a library such that at least 10^7 unique pairs of a DBD recognition element and a fusion protein could be tested for interaction.

213. The method of claim 211, wherein the DBD recognition element is part of a library of at least 10^8 members, the fusion protein is part of a library of at least 10^8 members, or the DBD recognition element and the fusion protein are both members of a library such that at

least 10^8 unique pairs of a DBD recognition element and a fusion protein could be tested for interaction.

214. The method of claim 205, wherein the host cell is a eukaryotic cell.

215. The method of claim 214, wherein the host cell is a yeast cell.

216. The method of claim 205, wherein the host cell is a prokaryotic cell.

217. The method of claim 216, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

218. The method of claim 205, wherein the host cells comprising a fusion protein that interacts with a DBD recognition element are isolated based on measuring a detectable signal conferred by a desired expression level of the reporter gene.

219. The method of claim 218, wherein the detectable signal is selected from the group consisting of color, fluorescence, luminescence and a cell surface tag.

220. The method of claim 205, wherein the DBD recognition element is a member of a library of binding sites for a DNA binding domain and host cells comprising a DBD recognition element bound by the polypeptide are isolated.

221. The method of claim 220, wherein the polypeptide is a zinc finger protein.

222. The method of claim 205, wherein the DBD recognition element is a desired binding site for a DNA binding domain and the test polypeptide is a member of a library and host cells comprising a polypeptide which binds to the DBD recognition element are isolated.

223. The method of claim 222, wherein the polypeptides are zinc finger proteins.

224. The method of claim 205, wherein the DBD recognition element is a member of library of potential binding sites for a DNA binding domain and the test polypeptide is a member of a library of polypeptides and host cells comprising a polypeptide that binds a DBD recognition element are isolated.

225. The method of claim 224, wherein the polypeptides are zinc finger proteins.

226. A polypeptide isolated by the method of any one of claims 205, 212, 213, 222 or 224.

227. The polypeptide of claim 226 which is a zinc finger protein.

228. A binding site for a DNA binding domain isolated by the method of any one of claims 205, 212, 213, 220 or 224.

229. The binding site for a DNA binding domain of claim 228 which binds a zinc finger protein.

230. An interacting pair of a polypeptide and a binding site for a DNA binding domain isolated by the method of any one of claims 205, 212, 213, 220, 222 or 224.

231. The interacting pair of claim 230, wherein the polypeptide is a zinc finger protein.

232. A method for selecting a polypeptide that differentially interacts with at least two different DNA sequences, comprising

i providing a population of host cells each of which contains

(a) a first reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a first DNA-binding domain,

(b) a second reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding site (DBD recognition element) for a second DNA-binding domain,

(c) a chimeric gene which encodes a fusion protein, the fusion protein including a test polypeptide and an activation tag,

wherein expression of the first and second reporter genes results in a signal detectable by FACS;

wherein interaction of a fusion protein with the first DBD recognition element in the host cells results in a desired level of expression of the first reporter gene;

wherein interaction of a fusion protein with the second DBD recognition element in the host cells results in a desired level of expression of the second reporter gene; and

ii isolating host cells comprising a fusion protein that interacts with the first DBD recognition element, the second DBD recognition element, or the first and second DBD recognition elements based on a desired level of expression of the first reporter gene, the second reporter gene, or the first and second reporter genes, respectively, using FACS, thereby selecting a polypeptide that differentially interacts with at least two different DNA sequences.

233. The method of claim 232, wherein fusion proteins are selected that interact to a desired extent with at least three different DNA sequences operably linked to reporter genes.

234. The method of claim 233, wherein fusion proteins are selected that interact to a desired extent with at least four different DNA sequences operably linked to reporter genes.

235. The method of claim 232, which further comprises the step of isolating the nucleic acid which encodes the fusion protein.

236. The method of claim 232, wherein each reporter gene may be detected independently, simultaneously, or independently and simultaneously.

237. The method of claim 232, wherein the desired level of expression of at least one of the reporter genes is an increase in reporter gene expression as compared to the basal expression level of the reporter gene.

238. The method of claim 232, wherein host cells are isolated which have one reporter gene whose level of expression is increased to a greater extent than the increase in the level of expression of the other reporter genes, relative to the basal expression level of the reporter genes.

239. The method of claim 232, which further comprises the step of isolating the nucleic acid which encodes the test polypeptides.

240. The method of claim 232, wherein the host cell is a eukaryotic cell.

241. The method of claim 240, wherein the host cell is a yeast cell.

242. The method of claim 232, wherein the host cell is a prokaryotic cell.

243. The method of claim 242, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

244. A method for detecting an interaction between a test RNA binding domain polypeptide and an RNA sequence, comprising

i providing a population of host cells wherein each cell contains

(a) a reporter gene operably linked to a transcriptional regulatory sequence which includes one or more binding sites (DBD recognition elements) for a DNA-binding domain,

(b) a first chimeric gene which encodes a fusion protein, the fusion protein including a DNA-binding domain and a first RNA binding domain,

(c) a second chimeric gene which encodes a fusion protein, the fusion protein including an activation tag and a second RNA binding domain,

(d) a third chimeric gene which encodes a hybrid RNA, the hybrid RNA comprising a first RNA sequence that binds one of the first or second RNA binding domains and a second RNA sequence to be tested for interaction with the RNA-binding domain not bound to the first RNA sequence;

wherein the expression of the reporter gene produces a signal detectable by FACS;

wherein interaction of an RNA-binding domain not bound to the first RNA sequence with the second RNA sequence in a host cell results in a desired level of expression of the reporter gene; and

ii isolating host cells comprising an RNA-binding domain that interacts with the second RNA sequence based on a desired level of expression of the reporter gene thereby detecting an interaction between a test RNA binding domain polypeptide and an RNA sequence using FACS.

245. The method of claim 244, which further comprises the step of isolating the nucleic acid which encodes the test RNA-binding domain polypeptide or the nucleic acid which encodes the portion of the RNA sequence bound by the test RNA-binding domain polypeptide.

246. The method of claim 244, wherein the host cell is a eukaryotic cell.

247. The method of claim 246, wherein the host cell is a yeast cell.

248. The method of claim 244, wherein the host cell is a prokaryotic cell.

249. The method of claim 248, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

250. A kit for selecting a polypeptide that interacts with a test polypeptide, comprising:

i a first gene construct for encoding a first fusion protein, which first gene construct comprises:

(a) transcriptional and translational elements which direct expression of a protein in a host cell,

(b) a DNA sequence that encodes a DNA binding domain and which is operably linked with the transcriptional and translational elements of the first gene construct, and

(c) one or more sites for inserting a DNA sequence encoding a first test polypeptide into the first gene construct in such a manner that the first test polypeptide is expressed in-frame as part of a fusion protein containing the DNA binding domain;

ii a second gene construct for encoding a second fusion protein, which second gene construct comprises:

(a) transcriptional and translational elements which direct expression of a protein in a host cell,

(b) a DNA sequence that encodes an activation tag and which is operably linked with the transcriptional and translational elements of the second gene construct, and

(c) one or more sites for inserting a DNA sequence encoding a second test polypeptide into the second gene construct in such a manner that the second test polypeptide is expressed in-frame as part of a fusion protein containing the activation tag;

iii a host cell containing at least one reporter gene having one or more binding sites (DBD recognition elements) for the DNA binding domain;

wherein expression of the reporter gene produces a signal detectable by FACS; and

wherein a desired level of expression of the reporter gene is obtained upon interaction of the first and second fusion proteins and can by analyzed using FACS.

251. The kit of claim 250, wherein the host cell is a eukaryotic cell.

252. The kit of claim 251, wherein the host cell is a yeast cell.

253. The kit of claim 250, wherein the host cell is a prokaryotic cell.

254. The kit of claim 253, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

255. The kit of claim 250, wherein the first, second, or first and second fusion proteins are a member of a library.

256. A test polypeptide isolated using the kit of claim 250.

257. A kit for detecting an interaction between a test DNA-binding domain polypeptide and a DNA sequence, comprising:

i a first gene construct which comprises:

(a) one or more sites for inserting a DNA sequence comprising a transcriptional element which includes at least one binding site (DBD recognition element) for a DNA-binding domain,

(b) a translational element operably linked to the transcriptional element, and

(c) a DNA sequence for at least one reporter gene which is operably linked with the transcriptional and translational elements of the first gene construct, and

wherein the transcriptional and translational elements direct expression of the reporter gene in a host cell;

ii a second gene construct for encoding a first fusion protein, which second gene construct comprises:

(a) transcriptional and translational elements which direct expression of a protein in a host cell,

(b) a DNA sequence that encodes an activation tag and which is operably linked with the transcriptional and translational elements of the second gene construct, and

(c) one or more sites for inserting a DNA sequence encoding a first test polypeptide into the second gene construct in such a manner that the first test polypeptide is expressed in-frame as part of a fusion protein containing the activation tag;

iii a host cell;

wherein expression of the reporter gene produces a signal detectable by FACS; and

wherein a desired level of expression of the reporter gene is obtained upon interaction of a test polypeptide with a DBD recognition element and can by analyzed by FACS.

258. The kit of claim 257, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, or a functional fragment of an RNA polymerase subunit.

259. The kit of claim 257, wherein the activation tag is an RNA polymerase, an RNA polymerase subunit, a functional fragment of an RNA polymerase, a functional fragment of an RNA polymerase subunit, a molecule covalently fused to RNA polymerase, a molecule covalently fused to an RNA polymerase subunit, a molecule covalently fused to a functional fragment of RNA polymerase, or a molecule covalently fused to a functional fragment of an RNA polymerase subunit.

260. The kit of claim 257, wherein the activation tag interacts indirectly with RNA polymerase via at least one intermediary polypeptide, nucleic acid, or small molecule, which functionally links the activation tag to the RNA polymerase.

261. The kit of claim 259, wherein the activation tag is a fragment of Gal 11P, and wherein the activation tag interacts with a fusion between Gal4 and the α subunit of RNA polymerase.

262. The kit of claim 257, wherein the host cell is a eukaryotic cell.

263. The kit of claim 262, wherein the host cell is a yeast cell.

264. The kit of claim 257, wherein the host cell is a prokaryotic cell.

265. The kit of claim 264, wherein the host cell is selected from the group consisting of bacterial strains of Escherichia, Bacillus, Streptomyces, Pseudomonas, Salmonella, Serratia, Streptococcus, Lactobacillus, Enterococcus and shigella.

266. The kit of claim 264, wherein the first, second, or first and second fusion proteins are a member of a library.

267. A test DNA-binding domain polypeptide isolated using the kit of claim 257.

268. The DNA-binding domain polypeptide of claim 267, which is a zinc finger protein.

269. A binding site for a DNA binding domain isolated using the kit of claim 257.

270. The binding site for a DNA binding domain of claim 269 that binds a zinc finger protein.

271. An interacting pair of a polypeptide and a binding site for a DNA binding domain isolated using the kit of claim 257.

272. The interacting pair of claim 271, wherein the polypeptide is a zinc finger protein.